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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,088	07/18/2001	Avi Ashkenazi	P1618P2C79	1981

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EXAMINER	
ANDRES, JANET L	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 12/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/909,088	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Janet L. Andres	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-47,49-52 and 55-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-47,49-52 and 55-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO AMENDMENT

1. Applicant's amendment filed 22 September 2003 is acknowledged. Applicant's correction is acknowledged; claims 39-47, 49-52, and 55-58 are pending and under examination in this application. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Rejections Withdrawn

2. The rejection of claims 39-47, 49-52, and 55-58 under 35 U.S.C. 101 is withdrawn in response to Applicant's arguments. The basis of the rejection is newly presented under 35 U.S.C. 112, below.

3. The rejection of claims 39-47, 49-52, and 55-58 under the judicially-created doctrine of obviousness-type double patenting is withdrawn in response to Applicant's filing of a terminal disclaimer.

Claim Rejections MaintainedNew Grounds of Rejection

4. Claims 39-47, 49-52, and 55-58 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte*

Forman, (230 USPQ 546 (Bd Pat. App. & Int. 1986)); *In re Wands,* 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Applicant states that the protein stimulates T cell proliferation in an MLR assay. Thus, the protein should be useful for stimulating T cell response in situations where such stimulation is desirable. However, Applicant has provided no evidence of a correlation between the *in vitro* stimulatory activity and a similar *in vivo* stimulation. The specification states only that the protein caused stimulation in an MLR. The MLR assay is a measure of alloreactivity of one individual to another individual, rather than a general measure of immune function. This reactivity is governed by the antigenic disparity between the two individuals that are being compared in the assay. The ability of the protein encoded by claimed invention to stimulate proliferation in the MLR assay may not be a general stimulus to lymphocyte proliferation, but rather a reaction to one of the MHC antigens on the responder cell. The instant specification fails to provide sufficient detail of the assay that was performed and fails to provide any data whatsoever in order for one of skill in the art to evaluate the conclusion that lymphocyte proliferation was stimulated by the encoded protein. In addition, the specification fails to provide any data or evidence of the results of the assay, therefore, one of skill in the art cannot evaluate the conclusion. The specification states that "positive increases over control are considered positive", however, this does not indicate that statistical significance must occur for determination of a positive result in the assay.

The art fails to teach that stimulation in an MLR is predictive of a similar *in vivo* result. Piccotti et al. (Transplantation 67: 1453-1460, 1999) demonstrates that IL-12 enhances alloantigen-specific immune function as determined by MLR, but this result *in vitro* does not

result in a measurable response *in vivo* (i.e. failure to accelerate allograft rejection) (see page 1459). Urso et al. (Cell. Mol. Biol. 41 suppl1: s103-112, 1995) teaches that zidovudine, which enhanced MLR response, was ultimately in fact immunosuppressive. Kond et al. (Immunology 79 : 459-464, 1993) teaches that TGF-β has both immunosuppressive and immuno-enhancing in such *in vitro* assays, but is immunosuppressive *in vivo*. Therefore, the MLR assay, which is art recognized for determining histocompatibility, does not appear to be predictive of general immune responses *in vivo*.

In conclusion, the results of the MLR assay do not provide sufficient guidance for one of skill to use the protein encoded by the claimed invention because the assay is not predictive of immune response in general, and one of skill in the art would not expect a stimulatory effect in the MLR assay to correlate to a general stimulatory effect on the immune system, absent evidence to the contrary. Thus, since the *in vitro* evidence provided by Applicant is not predictive of an *in vivo* effect, and since no conditions are known for which PRO335 could be used, it would require undue experimentation for the skilled artisan to use the invention.

The claims were previously rejected under 35 U.S.C. 101 as lacking utility. It was stated in the rejection of 20 May 2003 that there is no information regarding the correlation of MLR to any real-life disease, and that there is no information regarding what subsets of immune responses or cell types are affected. In the response of 22 September 2003, Applicant argues that the MLR is a well-established assay for assessing the ability of a test compound to stimulate or suppress T cell proliferation, and consequently the immune response of an individual and refers to a standard text. Applicant additionally argues that MLR is considered to be the best *in vitro* model for GVHD and graft rejection. Applicant argues that MLR has been used to identify

immunostimulators, which are desirable for cancer treatment, and that patients with AIDS demonstrate impaired autologous MLR. Applicant argues that the antibodies are thus useful for suppressing harmful proliferation, as in graft rejection or graft vs. host disease, and that the proteins are useful for stimulating T cell response, for example in leukemia, other cancers, and in immunocompromised patients such as AIDS sufferers.

Applicant's arguments are sufficient to indicate that MLRs are widely used and that an MLR can indicate, generally, that a compound with activity in such an assay might be of interest for study as an immunomodulator. However, as stated above, the assay does not provide sufficient guidance as to how one might use such a compound therapeutically and such a therapeutic use is the only asserted use for PRO 335. Applicants have supplied nothing to indicate that PRO335 is involved in any proliferative disease or that it has any role in graft rejection. The art cited by Applicant does not indicate that MLR has ever been directly used to identify a useful stimulator; one reference is concerned with the ability of certain cells to stimulate proliferation, and the other indicates that AIDS patients have a depressed MLR response. Thus while Applicant's teachings indicate that PRO 335 might be worth of further study, one of skill in the art would not be able to predict, based on Applicant's teachings and those in the art, that a compound identified only as having a stimulatory effect on in an MLR could be used for any condition *in vivo*.

5. The rejection of claims 39-43, 52, and 55-58 under 35 U.S.C. 112, first paragraph, as lacking enablement for and written description of variants is maintained for reasons of record in the office action of 20 May 2003.

Applicant argues that the functional limitation is meaningful for the reasons set forth in the response to the rejection of the claims under 35 U.S.C. 101. Since the functional limitation is not considered to be sufficient for the reasons set forth above, the rejection is maintained.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Andres, Ph.D., whose telephone number is (703) 305-0557. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564. The fax phone number for this group is (703) 872-9306 or (703) 872-9307 for after final communications.

Communications via internet mail regarding this application, other than those under U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[yvonne.eyler@uspto.gov]**.

All Internet email communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet Andres, Ph.D.
December 16, 2003